Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 2

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9. (Amended) The method of claim 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.

REMARKS

Claims 1-12 are stated to be pending in the instant application and have been rejected. However, it is respectfully pointed out that Claims 1-13 are actually pending. A replacement claim set was provided and published in the PCT application. This claim set was used for entry into the U.S. National Pahse. Applicants are responding based on this claim set. In response, the Applicants have amended claim 9. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Priority

Priority to parent application 09/181,601 has not been granted because the parent lacks descriptive support for the element of "NOESY-assign process". Applicants respectfully request reconsideration.

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 3

MPEP § 201.08 states that a continuation-in-part may be filed during the lifetime of an earlier nonprovisional application, repeating some substantial portion or all of the earlier nonprovisional and *adding matter not disclosed* in the said earlier nonprovisional application.

The current application shares a substantial portion of content and claims of the parent application 09/181,601. In particular, the steps of determining a biochemical function of a protein or polypeptide domain are identical. Both applications share the basic steps of identifying a putative polypeptide domain; determining three dimensional structure of the stable polypeptide domain; comparing the determined three dimensional structure of the stable polypeptide domain to known three-dimensional structures in a protein data bank; and correlating a biochemical function corresponding to the identified homologous structure to a biochemical function for the stable polypeptide domain. While the limitation of "NOESY-assign process" is a means of determining the three-dimensional structure of the stable polypeptide domain provided in this continuation-in-part application, this application is entitled to the benefit of priority of the parent application as the parent and instant

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 4

invention are drawn to a method of determining biochemical function of a protein or polypeptide domain of unknown function.

II. Rejection of Claim 9 Under 35 U.S.C. § 112

Claim 9 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner indicates that claim 9 improperly depends on a later claim, claim 11. Accordingly, Applicants have amended claim 9 to make reference to the third computer algorithm provided in claim 8. Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 12 has been rejected under 35 U.S.C. § 102(b) as being anticipated by the University of Texas at Galveston campus as evidenced by Mumenthaler et al. (*J. Mol. Biol.* (1995) 254:465-480). Applicants respectfully traverse this rejection.

In accordance with MPEP § 2131, the reference must teach every element of the claim. Mumenthaler et al. do not teach every element of the claimed method. In particular, Mumenthaler

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 5

et al. do not teach the steps of parsing a target polynucleotide
into at least one putative domain encoding region nor
subsequently expressing said putative domain on which to conduct
NMR analysis. Moreover, the proteins analyzed by Mumenthaler et
al. had **known** functions to which a three dimensional protein
structure was assigned. Claim 12 is directed toward the
determination of a biological function of a protein or protein
domain of **unknown** function. Nowhere, do Mumenthaler et al. teach
or suggest a method for determining biochemical function of a
protein or polypeptide domain of **unknown** function.

    Since Mumenthaler et al. do not teach a method wherein
polypeptide domains are identified and expressed and the unknown
function of said domain is determined, this reference can not
anticipate claim 12. Withdrawal of this rejection is therefore
respectfully requested.

**IV. Rejection of Claims 1, 5-9, 11 and 13 under 35 U.S.C. §
103(a)**

    Claims 1, 5 and 11 have been rejected under 35 U.S.C. §
103(a) as being unpatentable over Wallace et al. (*Protein Science*
(1996) 5:1001-1013) in view of Mumenthaler et al. (*J. Mol. Biol.*

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 6

(1995) 254:465-480). The Examiner suggests that it would have

been *prima facie* obvious to one of ordinary skill in the art at

the time this invention was made to combine the 3-D structural

alignment and function determination method of Wallace et al.

with the NOESY assignment method of Mumenthaler et al. since

Mumenthaler et al. state "We regard our method as a highly

practical tool for automatic calculation of three dimensional

protein structures from NMR spectra with minimal human interface

(abstract)". The Examiner suggests that an ordinary practitioner

would have been motivated to determine the 3-D structures used by

Wallace et al. for analysis by the automated method of

Mumenthaler et al. since the method is a highly practical tool

which results "In practice, the work required to assign NOESY

spectra is dramatically reduced by applying our automated method

(page 466, column 2)".

Claims 1-5 and 11 have been rejected under 35 U.S.C. 103(a)

as being unpatentable over Wallace et al. in view of Mumenthaler

et al. and further in view of Farber et al. (*J. Mol. Biol.* (1992)

226:471-479). The Examiner suggests that it would have been *prima*

facie obvious to one of ordinary skill in the art at the time the

invention was made to combine the method of Wallace et al. in

view of Mumenthaler et al. with the database preparation method

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 7

of Farber et al. since Farber et al. note "Simple neural networks

predict coding regions in DNA very well when trained on a

representation of DNA using single codon frequencies" (Page 478,

column 1)." The Examiner suggests that an ordinary practitioner

would have been motivated to combine the method of Wallace et al.

in view of Mumenthaler et al. with the protein coding

determinations of Farber et al. in order to maximize the usable

databases to identify homologous proteins and thereby determine

the function of unknown proteins.

Claims 1, 5, 6 and 11 have also been rejected under 35

U.S.C. § 103(a) as being unpatentable over Wallace et al. in view

of Mumenthaler et al. and further in view of Friedrichs et al.

(J. Biomol. NMR (1994) 4:703-726). The Examiner suggests that it

would have been *prima facie* obvious to one of ordinary skill in

the art at the time the invention was made to combine the 3-D

structural alignment and function determination method of Wallace

et al. in view of Mumenthaler et al. with the use of NMR

structural determination of Friedrichs et al. since Wallace et

al. state "This suggests that the development of databases of 3-D

templates, such as those that currently exist for protein

sequence templates, will help identify the functions of new

protein structures as they are determined and pinpoint their

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 8

functionally important regions (abstract)". The Examiner suggests

that the ordinary practitioner would have been motivated to

utilize NMR to determine protein structures in order to

sensitively and accurately provide data for 3-D determinations

and would have been motivated to utilize the automated

assignments of Friedrichs et al. in order to minimize the time

needed to determine the 3-D structure as expressly motivated by.

Friedrichs et al.

    Claims 1, 5, 7 and 11 have also been rejected under 35

U.S.C. § 103(a) as being unpatentable over Wallace et al. in view

of Mumenthaler et al. and further in view of Bagby et al. (J.

Biomol. NMR (1997) 10:279-282). The Examiner suggests that it

would have been prima facie obvious to one of ordinary skill in

the art at the time the invention was made to combine the button

test of Babgy et al. with the NMR and functional determination

method of Wallace et al. in view of Mumenthaler et al. since

Bagby et al. state "The button test is an efficient, small scale

way of tackling this problem (page 281, column 1)". The Examiner

suggests that the ordinary practitioner would have been motivated

to utilize the button test to optimize solubility for NMR since

it is expressly noted as efficient and small scale, which reduced

Attorney Docket No.:   RU-0115
Inventors: **Anderson et al.**
Serial No.:   09/744,002
Filing Date: **August 2, 2001**
Page 9

time and wasted reagents, which for purified proteins can
represent a large investment of time and money.

Claims 1, 5 and 8-11 have also been rejected under 35 U.S.C.
§ 103(a) as being unpatentable over Wallace et al. in view of
Mumenthaler et al. and further in view of Holm et al. (*TIBS*
(1995) 20:478-480). The Examiner suggests that it would have been
prima facie obvious to one of ordinary skill in the art at the
time the invention was made to combine the 3-D structural
alignment and function determination method of Wallace et al. in
view of Mumenthaler et al. with the NMR technique taught by Holm
et al. and well known in the art for structure determination
purposes and with the use of domains within the range of 50-300
amino acids since Holm et al. teach screening domain of those
sizes. The Examiner suggests that the ordinary practitioner would
have been motivated to utilize database analysis of Holm et al.
in mind of Wallace et al. since Wallace et al. state "As the
number of known protein structures increases, so the need for a
3-D equivalent of PROSITE grows with it, especially for likely
functions of proteins whose biological role is unknown (page
1001, column 1)." Further, Wallace et al. note that there is a
need for methods of 3-D comparison of proteins in order to
determine the biochemical function of unknown proteins. Holm et

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 10

al. state "At the last stages of solving a new protein structure,
crystallographers and nuclear magnetic resonance (NMR)
spectroscopists are keen to know if their structure represents a
unique protein fold or if it has an unexpected structural
similarity to a known protein fold. To answer these questions,
the DALI server performs a database search with a new structure
against all structures in the Protein Data Bank (Page 478, column
3)". Thus, the Examiner further suggests that the ordinary
practitioner would have been motivated to perform a comparison to
determine the relationship of the new protein with proteins
present in the database, thereby fulfilling the stated need and
motivation of Wallace et al.

Claims 1, 5, 8-11 and 13 have also been rejected under 35
U.S.C. § 103(a) as being unpatentable over Wallace et al. in view
of Mumenthaler et al. and further in view of Holm et al. and
further in view of Farber et al. The Examiner suggests that it
would have been *prima facie* obvious to one of ordinary skill in
the art at the time the invention was made to combine the method
of Wallace et al. in view of Mumenthaler et al. and further in
view of Holm et al. with the database preparation method of
Farber et al. since Farber et al. note "Simple neural networks
predict coding regions in DNA very well when trained on a

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 11

representation of DNA using single codon frequencies (page 478,

column)." The Examiner further suggests that the ordinary

practitioner would have been motivated to combine the method of

Wallace et al. in view of Mumenthaler et al. and further in view

of Holm et al. with the protein coding determinations of Farber

et al. in order to maximize the usable databases to identify

homologous proteins and thereby determine the function of unknown

proteins.

    Applicants respectfully traverse these rejections.

    MPEP § 2143 states that to establish a *prima facie* case of

obviousness, three basic criteria must be met. First, there must

be some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of

ordinary skill in the art to modify the reference or combine the

reference teachings. Second, there must be a reasonable

expectation of success. Finally, the prior art references when

combined must teach or suggest all the claim limitations. The

teaching or suggestion to make the claimed combination must both

be found in the prior art, and not based on the applicant's

disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.

1991).

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 12

The primary reference of Wallace et al. does not teach an essential step in the method of claim 1, namely the identification of protein or polypeptide domain that properly folds into a stable polypeptide domain with a defined three dimensional structure. Nor is there any suggestion of this step as Wallace et al. teach the use of a triad of amino acids and a protein structure database to identify function of proteins with a known structure. Nowhere does the primary reference teach or provide the skilled artisan with the motivation to take a single- or multi-domain protein or polypeptide of unknown function and identify each individual domain of said protein or polypeptide. Thus, the primary reference also fails to provide any teaching or suggestion of the system of claim 13 which comprises the identification of at least one putative polypeptide domain (element A) prior to the steps of expressing the domain and determining its three dimensional structure.

Secondary references cited in these obviousness rejections fail to remedy the deficiencies in the primary reference.

As discussed in Section III, *supra*, Mumenthaler et al. teach automated assignment of NOESY spectra. Thus, this reference also provides no teaching or suggestion with respect to the essential step of identifying protein or polypeptide domains.

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 13

Farber et al. disclose a neural network and information-theory for determination of coding regions for eukaryotic proteins in raw sequence base information. Only the hindsight vision afforded by the claimed invention would motivate the skilled practitioner to combine the teachings of Wallace, et. and Farber et al.

The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. MPEP §2143.01. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Wallace et al. is a protein biochemistry article directed at the analysis of protein-structure and function. Contrary to the Examiner's suggestion, it would not have been obvious to the ordinary protein biochemist after reading Wallace et al. to take the additional steps provided by Farber et al. of mining a polynucleotide-database and predicting exon boundaries in a polynucleotide sequence. Furthermore, the combination of Wallace et al. with Farber et al. still does not provide the essential step of identifying protein or polypeptide domains. Thus, Farber et al. alone is insufficient for determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 14

     The teachings of Friedrichs et al. are related to an automated system for protein ^{15}N, ^{13}C, and ^{1}H NMR resonance assignments from a set of three-dimensional NMR spectra. While resonance assignments are useful in establishing the three dimensional structure of protein, this information alone is insufficient for three dimensional structure determination. Accordingly, this reference also provides no teaching or suggestion with respect to either identification of protein or polypeptide domains or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

     Similarly, Bagby et al. fail to teach or suggest these claim limitations. As acknowledged by the Examiner, the teachings of Bagby et al. are related to preparation of samples for NMR analysis and do not provide the identification of protein or polypeptide domains or the determination of unknown function of unknown three-dimensional protein structures as claimed in the instant invention.

     The reference of Holm et al. is a commentary article wherein the DALI method is disclosed as useful for studying protein structure. Accordingly, this reference also provides no teaching or suggestion with respect to either identification of protein or

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 15

polypeptide domains or the determination of unknown function of

unknown three-dimensional protein structures as claimed in the

instant invention.

As set forth by both the Court of Appeals for the Federal

Circuit and the MPEP, when an independent claim is nonobvious

under 35 U.S.C. §.103, then any claim depending therefrom is

nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988) and MPEP § 2143.03. Thus, while some of the secondary

references may teach or suggest specific elements as set forth in

the dependent claims, the cited combination of references fail to

teach or suggest all the limitations of the method or system as

set forth in independent claims 1, 12 and 13. Accordingly, the

cited combinations of prior art references can not render obvious

the instant claimed invention. Withdrawal of these rejections is

therefore respectfully requested.

V.   Conclusion

Applicants believe that the foregoing comprises a full and

complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending

claims is earnestly solicited.

Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 16

·Attached hereto is a marked-up version of the changes made

to the claims by the current amendment. The attached page is

captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

                              Respectfully submitted,

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Attorney Docket No.:   **RU-0115**
Inventors: **Anderson et al.**
Serial No.:   **09/744,002**
Filing Date: **August 2, 2001**
Page 17

VERSION WITH MARKINGS TO SHOW CHANGES MADE

<u>In the Claims</u>:

Claim 9 has been amended as follows:

9. (Amended) The method of claim ~~11~~ 8, wherein said third computer algorithm is selected from the group consisting of DALI, CATH and VAST.